Reumatizam 2021;68(1):45–49
https://doi.org/10.33004/reumatizam-68-1-5

CASE REPORT PRIKAZ BOLESNIKA

LATE-ONSET OF SYSTEMIC SCLEROSIS – CASE REPORT AND LITERATURE REVIEW

SISTEMSKA SKLEROZA KOD STARIJEG BOLESNIKA – PRIKAZ BOLESNIKA I PREGLED LITERATURE

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Received / Primljeno: March 8, 2021 / 8. 3. 2021.
Accepted / Prihvaćeno: June 16, 2021 / 16. 6. 2021.

Abstract

Systemic sclerosis most commonly occurs in middle-aged patients. Younger or older people are rarely affected. It is very rare in people over the age of 80. In older patients, different clinical and laboratory characteristics of the disease, as well as a different therapeutic response are expected, in comparison to younger patients. Therefore, we present the case of an 84-year-old patient with systemic sclerosis, as well as a literature review in relation to this topic.

Key words: Systemic sclerosis; Geriatrics; Glucocorticoids

Sažetak

Sistemska skleroza se najčešće javlja u bolesnika srednje životne dobi. Rjeđe obolijevaju mlađe ili starije osobe, a vrlo rijetko se javlja u osoba starijih od 80 godina. U starijih bolesnika možemo očekivati drugačija klinička i laboratorijska obilježja bolesti kao i terapijski odgovor u odnosu na mlađe bolesnike. Stoga, u ovom radu prikazujemo 84-godišnjeg bolesnika sa sistemskom sklerozom, uz pregled literature o ovoj temi.

Ključne riječi: Sistemska skleroza; Gerijatrija; Glukokortikoidi

INTRODUCTION

Systemic sclerosis (SSc) is a systemic inflammatory rheumatic disease characterised by the presence of fibrosis of the skin and internal organs and obliterative vasculopathy in addition to immune system disorders. The disease usually occurs in women between the ages of 30 and 50, while it is a less common occurrence in

UVOD

Sistemska skleroza (SSc) sistemska je upalna reumatska bolest koju uz imunološke abnormalnosti karakterizira prisutnost fibroze kože i unutarnjih organa te obliterirajuća vaskulopatija. Bolest se obično javlja u žena u dobi između 30 i 50 godina, dok je u muškaraca i u osoba starije životne dobi znatno rjeđa. Istraživanja

men and the elderly. Studies have shown that clinical features differ between patients who develop the disease at a younger age compared to geriatric patients (1).

Elderly patients have an increased risk of developing pulmonary hypertension, heart and kidney failure, and pronounced muscle weakness and functional impairment. While comparing the laboratory findings of older and younger patients, high levels of alkaline phosphatase (ALP) and low levels of creatinine kinase (CK) were observed in older patients, as well as a high percentage of anti-centromere antibodies and low level of U1RNP antibodies, which were observed in immunological findings. On the other hand, elderly patients tend to have a mild form of Raynaud's phenomenon as well as a lower risk of developing digital ulcers (2).

There is no doubt that high life expectancy in patients with SSc is associated with a poor prognosis, but it is important to note that most geriatric patients have other comorbidities which, in addition to the age factor, increase the risk of adverse outcomes and mortality.

In this paper, we shall present the case of an 84-year-old patient who came for a check-up due to pain and swelling of the small wrist joints with significantly reduced functional ability, and who was eventually diagnosed with SSc.

CASE REPORT

An eighty-four-year-old patient was referred for specialist treatment due to symptoms such as swelling and pain in his fingers and Raynaud's phenomenon, which appeared several months ago. Various conditions such as arterial hypertension, coronary heart disease (after recovery from myocardial infarction) and scalp sarcoma surgery which occurred several years ago (without chemotherapy) were known from the patient's medical history.

The clinical examination revealed abnormalities such as diffuse swelling of the fingers ("puffy fingers"), arthritis of the small wrist joints and both wrists, sclerodactyly, skin tightening of the upper extremities and chest, and all of these symptoms were enough to diagnose SSc based on the clinical features. Extremely high levels of inflammatory markers were observed in laboratory findings (ESR = 102 mm/hr, CRP = 81 g/L). Subsequent immunological findings included a positive antinuclear antibody finding with positive centromere-specific fluorescence (> 1: 640). The CK finding was in the normal range (21 U/L). Capillaroscopy revealed the presence of megacapillaries and pathological bleeding, which indicated an active scleroderma pattern. Pulmonary function tests showed reduced diffusion capacity for carbon monoxide (DLCO = 57%), and multi-slice computed tomography (MSCT) findings of the chest did not show a distinct interstitial pattern. The echocardiogram showed signs of ischemic

su pokazala da se klinička obilježja razlikuju između bolesnika kod kojih se bolest pojavi u mlađoj dobi u odnosu na gerijatrijske bolesnike (1).

U starijih bolesnika povećan je rizik za nastanak plućne hipertenzije, srčano i bubrežno oštećenje, a izraženija je mišićna slabost i funkcionalna onesposobljenost. U laboratorijskim nalazima, u odnosu na mlađe bolesnike, u starijih bolesnika uočene su više vrijednosti alkalne fosfataze (ALP) i niže vrijednosti kreatinin kinaze (CK), a u imunološkim nalazima veći postotak pozitivnih protutijela na centromere i manja prisutnost U1RNP protutijela. S druge strane, bolesnici starije životne dobi obično imaju blaži oblik Raynaudovog fenomena kao i manji rizik za nastanak digitalnih ulceracija (2).

Nedvojbeno je da je visoka životna dob u bolesnika sa SSc-om povezana s lošijom prognozom, ali važno je naglasiti da većina gerijatrijskih bolesnika ima pridružene i druge komorbiditete koji zajedno sa životnom dobi sami po sebi povisuju rizik lošijeg ishoda i smrtnosti.

U ovom radu prikazujemo bolesnika u dobi od 84 godine koji se javio na pregled zbog bolova i oteklina malih zglobova šaka uz značajno reduciranu funkcionalnu sposobnost, a kojemu je u konačnici dijagnosticiran SSc.

PRIKAZ BOLESNIKA

Osamdesetčetverogodišnji bolesnik upućen je na specijalističku obradu zbog pojave oteklina i bolova prstiju šaka te Raynaudovog fenomena unatrag nekoliko mjeseci. Iz ranije anamneze bila je poznata arterijska hipertenzija, koronarna bolest srca (stanje nakon preboljelog infarkta miokarda) te operacija sarkoma na vlasištu prije više godina (bez provedene kemoterapije).

U kliničkom pregledu dominirale su difuzne otekline prstiju šaka (engl. "*puffy fingers*"), artritis malih zglobova šaka i obaju ručnih zglobova, sklerodaktilija, zategnutost kože gornjih ekstremiteta i prsnog koša, što je bilo dovoljno da se već na osnovi kliničke slike postavi dijagnoza SSc-a. U laboratorijskim nalazima zabilježene su izrazito povišene vrijednosti rekatanata upale (SE=102 mm/h, CRP= 81 g/L). U naknadno pristiglim imunološkim nalazima bila su visoko pozitivna antinuklearna protutijela s pozitivnom fluorescencijom na centromere (>1:640). Nalaz CK je bio uredan (21 U/L). Kapilaroskopski, prisutne su megakapilare te zone patološkog krvarenja, što je upućivalo na aktivni sklerodermijski uzorak. Testovi plućne funkcije pokazali su smanjen difuzijski kapacitet za ugljični monoksid (DLCO=57%), a nalaz kompjuterizirane tomografije (MSCT) toraksa nije pokazao značajan intersticijski uzorak tipičnih promjena. Ultrazvukom srca zabilježeni su znakovi ishemijske kardiomiopatije uz održanu ejekcijsku frakciju, dok nije nađeno indirektnih znakova plućne hipertenzije. Radiografska pasaža jednjaka

cardiomyopathy with preserved ejection fraction, while no indirect signs of pulmonary hypertension were detected. The barium swallow test of the oesophagus showed no abnormalities, the chest MSCT showed no signs of oesophageal dilatation, the patient had no pronounced gastrointestinal disturbances, and did not agree to the recommended endoscopy. Tumour markers and abdominal magnetic resonance imaging showed no signs of associated active malignancy. Therapy was initiated by administering low doses of methylprednisolone (8 mg of methylprednisolone for two weeks, followed up with a dose of 4 mg for 5 months and ultimately a dose of 4 mg every other day) and peripheral vasodilators (amlodipine). There was an excellent clinical response to this therapy, in addition to the regression of peripheral arthritis and swelling of the fingers, as well as the regression of skin thickening. Normalisation of inflammatory parameters is observed in laboratory findings. At the follow-up appointments, the patient was in good general condition, his functional status was normal, and he was able to perform all normal daily activities. We continue to carry out the follow-up of this patient.

DISCUSSION

This paper presents the case of a patient who was diagnosed with SSc at the age of 84. Through this case report, it can be concluded that the clinical and laboratory characteristics of SSc, according to the data found in the reviewed literature, were different in the case of our geriatric patient compared to younger patients. SSc is a disease that most commonly occurs in the working age population, although its incidence has been reported in both younger and older patients. A relatively small number of cases in which patients were diagnosed with SSc late in life has been described in literature so far.

Hügle et al. have conducted a study which included 8554 patients with SSc. Out of the total number of patients, only 123 of them (1.4%) were older than 75, and the results showed that the elderly patients were more likely to have a limited type of SSc and a higher prevalence of anti-centromere antibodies. The modified Rodnan skin score and the prevalence of pulmonary fibrosis did not differ significantly between the two groups (3). According to the 2013 ACR/EULAR classification criteria, the skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints is sufficient for the patient to be classified as having SSc. In the case of our patient, it was determined at the first clinical examination that there were enough elements to raise suspicion of SSc. Other manifestations of the disease that collectively confirm the diagnosis of SSc (score ≥9) include: skin thickening of the fingers, fingertip lesions, telangiectasia, abnormal

bila je uredna, MSCT toraksa nije pokazao dilataciju jednjaka, bolesnik nije imao izraženih gastrointestinalnih smetnji, a nije bio sklon preporučenoj endoskopskoj obradi probavnog trakta. Tumorski markeri i magnetska rezonancija abdomena nisu pokazali znakova pridružene aktivne maligne bolesti. Započeta je terapija niskim dozama metilprednizolona (8 mg metilprednizolona kroz dva tjedna, zatim nastavljeno 4 mg kroz 5 mjeseci i nakon toga nastavljeno 4 mg svaki drugi dan) i perifernim vazodilatatorima (amlodipin). Na navedenu terapiju nastupio je odličan klinički odgovor, regresija perifernog artritisa i oteklina prstiju šaka, kao i regresija kožnog zadebljanja. U laboratorijskim nalazima prati se normalizacija upalnih parametara. Na kontrolama je bolesnik dobroga općeg stanja kao i funkcionalnog statusa, obavlja sve uobičajene aktivnosti. Bolesnik je u našem daljnjem praćenju.

RASPRAVA

U ovom radu prikazan je bolesnik kojemu je u 84. godini postavljena dijagnoza SSc-a. Prikazom slučaja može se zaključiti da su kliničko-laboratorijska obilježja SSc-a, sukladno podatcima iz literature, i kod našeg gerijatrijskog bolesnika bila različita u odnosu na bolesnike mlađe životne dobi. SSc je bolest koja se najčešće javlja u radno aktivnoj populaciji, iako je njezina pojavnost opisana i kod mlađih i starijih pacijenata. U literaturi je do sada opisan relativno mali broj bolesnika koji su od SSc-a oboljeli u starijoj životnoj dobi.

Hugle i sur. proveli su istraživanje na 8.554 pacijenta sa SSc-om, od kojih su samo 123 bolesnika (1,4%) bili stariji od 75 godina i pokazali su kako stariji bolesnici češće imaju limitirani oblik bolesti i veću prevalenciju antitijela na centromere. Modificirani Rodnanov kožni zbroj i prevalencija plućne fibroze nisu se značajno razlikovali između dvije skupine (3). Prema ACR/EULAR kriterijima iz 2013. godine, zadebljanje kože prstiju obje ruke proksimalno od metakarpofalangealnih zglobova dovoljno je za klasifikaciju pacijenta za dijagnozu SSc-a. U našeg bolesnika temeljem kliničkog pregleda bilo je dovoljno elemenata da se već prvim pregledom postavi temeljita sumnja na SSc. Ostale manifestacije bolesti čijim se zbrajanjem određuje potvrda dijagnoze bolesti (skor ≥9) jesu: zadebljanje kože prstiju, lezije vrškova prstiju, telangiektazije, kapilaroskopski abnormalne kapilare ležišta noktiju, plućna arterijska hipertenzija i/ili intersticijska bolest pluća, Raynaudov fenomen i autoantitijela povezana sa SSc-om (4). U našeg bolesnika bila je prisutna sklerodaktilija, Raynaudov fenomen, u laboratorijskim nalazima visoko pozitivna protutijela na centromere, dok je nalaz kapilaroskopije pokazao aktivan sklerodermijski uzorak.

Prema objavljenim podatcima, plućna hipertenzija dijagnosticirana ultrazvukom i kateterizacijom desnog srca češća je u bolesnika s kasnim početkom bolesti,

nailfold capillaries (detected through capillaroscopy), pulmonary arterial hypertension and/or interstitial lung disease, Raynaud's phenomenon and SSc-related autoantibodies (4). Our patient had sclerodactyly and Raynaud's phenomenon, a positive anti-centromere antibody finding (a type of anti-nuclear antibodies) was revealed through laboratory findings, while capillaroscopy revealed an active scleroderma pattern.

According to the published literature data, pulmonary hypertension diagnosed with an echocardiogram and right heart catheterisation are more common in patients with late onset of the disease, while the risk of digital ischemia is lower in these patients. The prevalence of anti-U1RNP antibodies is significantly lower in elderly patients (2). The ultrasound showed no signs of pulmonary hypertension in our patient, and according to the data found in the literature, the anti-U1RNP antibodies were negative. Despite the Raynaud's phenomenon and an active scleroderma pattern (revealed through capillaroscopy), digital ulcerations were not present in our patient.

Gastrointestinal involvement is relatively high in patients with SSc. In a study conducted by Alba et al., patients with early onset of the disease have been shown to have a higher prevalence of oesophageal involvement (72% of early-onset patients compared to 56% of late-onset patients). After correction for the population effects of age and sex, mortality was shown to be higher in younger patients (1). The patient from this case report had no gastroenterological disorders or symptoms or signs typical of SSc, the barium swallow test of the oesophagus showed no abnormalities, and the chest MSCT showed no signs of oesophageal dilatation.

In our patient, high levels of alkaline phosphatase (ALP) and relatively low levels of creatinine kinase (CK) were recorded, in accordance with the data found in the literature (5).

Although it seemingly appeared like a typical clinical presentation of SSc, our patient's case required additional caution and differential diagnosis, primarily due to the presence of extremely high inflammatory markers and pronounced Raynaud's phenomenon, which could indicate an associated malignancy. It is important to note that Raynaud's phenomenon could be one of the initial manifestations of an associated malignancy (6).

An earlier diagnosis of a malignancy that was cured several years ago is unlikely to be associated with the development of SSc, and our patient has not been treated with chemotherapy or other drugs that would be associated with the development of SSc.

It is interesting to note that in the treatment of our patient, a low dose of glucocorticoids led to a complete regression of clinical symptoms as well as an improvement in skin manifestations, i.e., it resulted in an almost complete remission of the disease.

dok je rizik od digitalne ishemije u tih bolesnika manji. Prevalencija anti-U1RNP antitijela znatno je rjeđa u bolesnika u starijoj dobi (2). U našeg bolesnika nije bilo ultrazvučnih znakova za plućnu hipertenziju, a sukladno podatcima iz literature anti-U1RNP protutijela bila su negativna. Unatoč prisutnom Raynaudovom fenomenu i kapilaroskopski aktivnom sklerodermijskom uzorku kod našeg bolesnika nisu bile prisutne digitalne ulceracije.

Zahvaćanje gastrointestinalnog sustava relativno je visoko u bolesnika sa SSc-om. U studiji Albe i sur. pokazano je da bolesnici s ranim početkom bolesti imaju veću prevalenciju zahvaćenosti jednjaka (72% pacijenata sa ranim početkom u usporedbi s 56% kod kasnog početka). Nakon korekcije za dob i spol, pokazalo se da je smrtnost veća kod mlađih bolesnika (1). Ovdje prikazani bolesnik nije imao gastroenteroloških smetnji odnosno simptoma ili znakova tipičnih za SSc, nalaz pasaže jednjaka bio je uredan, a na MSCT-u toraksa nije se vidjelo dilatacije jednjaka.

U našeg bolesnika zabilježene su više vrijednosti ALP-a i relativno niže vrijednosti CK-a, a sukladno podatcima iz literature (5).

Iako naizgled tipična klinička prezentacija SSc-a, u našeg bolesnika bio je potreban dodatan oprez i diferencijalna dijagnostička obrada, a prvenstveno zbog prisutnih izrazito visokih upalnih biljega i izraženog Raynaudova fenomena, koji bi mogli upućivati i na pridruženu malignu bolest, a čija prva manifestacija može biti upravo Raynaudov fenomen (6).

Ranija dijagnoza izliječene maligne bolesti prije više godina vjerojatno nema poveznice s razvojem SSc-a, a naš bolesnik nije liječen kemoterapijom ili drugim lijekovima koji bi bili povezani s nastankom SSc-a.

Zanimljiv je podatak da je u liječenju našeg bolesnika niska doza glukokortikoda dovela do potpune regresije kliničkih simptoma kao i poboljšanja kožnih manifestacija, odnosno gotovo do remisije bolesti.

Planira se daljnja redukcija odnosno pokušaj isključivanja glukokortikoida, a u slučaju nepovoljnoga kliničkog odgovora razmotrit će se primjena drugih imunosupresiva čija primjena nije limitirana u starijih bolesnika, ali potrebna je prilagodba doze lijekova bubrežnoj i jetrenoj funkciji uzimajući u obzir sve pridružene komorbiditete kod starijih bolesnika.

Za razliku od povoljnog tijeka bolesti i dobrog odgovora na terapiju koji smo imali u našeg bolesnika, SSc kasnije pojavnosti uglavnom se povezuje s agresivnijim oblikom bolesti (3).

Veća prevalencija ekstrakutanog zahvaćanja organa u početku bolesti i ranija pojava sistemskih manifestacija u starijih osoba vjerojatno je razlog ranijeg započinjanja obrade i postavljanja dijagnoze (1,2,7). Potrebno je obratiti pozornost i na skupinu mlađih pacijenata s blažim simptomima koji su u početku klasificirani

Further reduction or an attempt of discontinuation of glucocorticoid therapy is planned, and in case of an adverse clinical response, other immunosuppressants, whose use is not limited in elderly patients, will be considered. However, the dose of these immunosuppressants should be adjusted in order to be in accordance with the renal and hepatic function, taking into account all comorbidities that may occur in elderly patients.

In contrast to the mild course of the disease and the good response to therapy we had in our patient, late-onset SSc is mainly associated with a more aggressive form of the disease (3).

The higher prevalence of extracutaneous organ involvement at the onset of the disease and the earlier occurrence of systemic manifestations in the elderly is the probable reason for the earlier initiation of treatment and diagnosis (1,2,7). Attention should also be paid to the group of younger patients with mild symptoms who were initially classified as cases of undifferentiated connective tissue disease and who tend to develop features of SSc later in life (8).

Although systemic sclerosis most often occurs in middle-aged people, its occurrence has also been reported in elderly patients. Clinical and laboratory characteristics as well as response to therapy are different in younger and older patients. There is no doubt that high life expectancy in patients with SSc is associated with a poor prognosis, but it is important to note that most geriatric patients have other comorbidities which, in addition to the age factor, increase the risk of adverse outcomes and mortality.

A relatively small number of cases with SSc onset in patients over the age of 80 has been described in literature so far. Our patient's case report enables a better exchange of clinical experiences, facilitation in differential diagnosis and a diagnostic and therapeutic algorithm in patients with late-onset SSc. It is particularly interesting to note that the administration of low doses of glucocorticoids in our patient has produced satisfactory results in terms of cutaneous manifestations of the disease, in addition to having a beneficial effect on peripheral joints. In addition to being significant in terms of scientific contribution, this patient's case report can also contribute to additional research into the pathophysiological mechanisms of the onset and progression of this disease in geriatric patients.

Conflict of interest statement: The authors declare no conflict of interest.

kao nediferencirana bolest vezivnog tkiva, a koji tek kasnije razvijaju značajke SSc-a (8).

Iako se sistemska skleroza najčešće javlja u osoba srednje životne dobi, njezina pojavnost zabilježena je i u starijih bolesnika. Kliničko-laboratorijska obilježja kao i odgovor na terapiju različiti su između mlađih i starijih bolesnika. Nedvojbeno je da je visoka životna dob u bolesnika s SSc-om povezana s lošijom prognozom, ali važno je naglasiti da većina starijih bolesnika ima pridružene i druge komorbiditete koji zajedno sa životnom dobi sami po sebi povećavaju rizik od lošijeg ishoda i smrtnosti.

U literaturi je do sada opisan ralativno mali broj bolesnika u kojih se SSc manifestirala u dobi iznad 80 godina. Prikaz našeg bolesnika omogućuje bolju razmjenu kliničkih iskustava, olakšanje u diferencijalnoj dijagnostici i dijagnostičko-terapijski algoritam u bolesnika s SSc-om starije životne dobi. Od posebnog je interesa da je uz povoljan učinak na periferne zglobove primjena niskih doza glukokortikoda u našeg bolesnika polučila dobre rezultate na kožne manifestacije bolesti. Osim stručnog doprinosa, prikaz ovog bolesnika može pridonijeti i dodatnim istraživanjima u patofiziološkim mehanizmima nastanka i progresije ove bolesti kod gerijatrijskih bolesnika.

Izjava o sukobu interesa: Autori izjavljuju da nisu u sukobu interesa.

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